From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 February 2001 (09.02.01)	
International application No. PCT/US00/15732	**Applicant's or agent's file reference** REG334-A-PCT
International filing date (day/month/year) 08 June 2000 (08.06.00)	**Priority date** (day/month/year) 17 June 1999 (17.06.99)
Applicant WIEGAND, Stanley, J.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

19 December 2000 (19.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
REG 334-A-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15732	08/06/2000	17/06/1999
International Patent Classification (IPC) or national classification and IPC A61K49/00		
Applicant REGENERON PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/12/2000	21.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giacobbe, S Telephone No. +49 89 2399 8463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/15732

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-37	as originally filed				

Claims, No.:

13-19,28-37	as originally filed				
1-12,20-27	as received on	06/07/2001	with letter of	05/07/2001	

Drawings, sheets:

1/5-5/5	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-21 (IA only).

because:

   ☒ the said international application, or the said claims Nos. 1-21 (IA only) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 1-37 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

1. Section I

The amended claims fulfill the requirements of Art 34(2)(b) PCT, in that they do not introduce subject-matter which was not present in the application as originally filed.

2. Section III

2.1 Claims 1-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2.2 This International Preliminary Examining Division is of the opinion that the present application totally lacks disclosure in the sense of Art 5 PCT, the reason being that it does not provide any example as to how the claimed invention can be carried out. The description illustrates an alleged discovery (and not an invention), namely the fact that Ang-2 plays a role in neovascularisation of tumours (cf. Examples), and goes then on to deduce that known molecules capable of detecting Ang-2 could play a role in tumour imaging or targeting (cf. p. 19, l. 8 to p. 20, ll. 22), but it does not actually show how this targeting or imaging can be done, so that the skilled person would have great difficulty in carrying out the subject-matter of the claims.

In accordance with the provisions of Art 34(4)(a)(ii) PCT this International Preliminary Examining Division shall therefore not go into the questions referred to in Art 33(1) PCT, namely the question of whether the claims are novel, involve an inventive step or are industrially applicable.

WE CLAIM

1. A method for imaging tumour associated vasculature at an early stage of tumour development in a mammal comprising

a) administering to the mammal a composition which comprises a molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an imaging agent;

b) allowing the composition to accumulate at the tumour vasculature; and

c) detecting the accumulated composition so as to image the tumour vasculature.

2. The method of claim 1 wherein the Ang-2 and the molecule capable of detecting Ang-2 are nucleic acids.

3. The method of claim 1 wherein the Ang-2 and the molecule capable of detecting Ang-2 are polypeptides.

4. The method of claim 1 wherein the accumulated composition is detected by a detector selected from the group consisting of a conventional scintillation camera, a gamma camera, a rectilinear scanner, a PET scanner, a SPECT scanner, a MRI scanner, a NMR scanner, and an X-ray machine.

5. The method of claim 1 wherein the imaging agent is a radionuclide or a chelate.

6. A method of causing tumour cell death by targeting tumour associated vasculature at an early stage of tumour development comprising administering to a mammal a composition which comprises a

molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an agent capable of causing tumour cell death.

7. A method of causing vascular endothelial cell death by targeting tumour associated vasculature at an early stage of tumour development comprising administering to a mammal a composition which comprises a molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an agent capable of causing vascular endothelial cell death.

8. The method of claim 6 wherein the Ang-2 and the molecule capable of detecting Ang-2 are nucleic acids.

9. The method of claim 7 wherein the Ang-2 and the molecule capable of detecting Ang-2 are nucleic acids.

10. The method of claim 6 wherein the agent capable of causing tumour cell death is selected from the group consisting of carboplatin, cisplatin, vincristine, methotrexate, paclitaxel, docetaxel, 5-fluorouracil, UFT, hydroxyurea, gemcitabine, vinorelbine, irinotecan, tirapazamine, and matrilysin.

11. The method of claim 6 wherein the Ang-2 and the molecule capable of detecting Ang-2 are polypeptides.

12. The method of claim 7 wherein the Ang-2 and the molecule capable of detecting Ang-2 are polypeptides.

20. The method of claim 2, 8, or 9 wherein the molecule capable of detecting Ang-2 nucleic acid is a synthetic oligonucleotide.

21. The method of claim 3, 11, or 12 wherein the molecule capable of detecting Ang-2 polypeptide is a synthetic polypeptide.

22. A kit for imaging tumour associated vasculature at an early stage of tumour development in a mammal comprising a composition which comprises a molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an imaging agent.

23. The kit of claim 22 wherein the Ang-2 and the molecule capable of detecting Ang-2 are nucleic acids.

24. The kit of claim 22 wherein the Ang-2 and the molecule capable of detecting Ang-2 are polypeptides.

25. A kit for targeting tumour associated vasculature at an early stage of tumour development in a mammal comprising a composition which comprises a molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an agent capable of causing tumour cell death.

26. A kit for targeting tumour associated vasculature at an early stage of tumour development in a mammal comprising a composition which comprises a molecule capable of detecting the early expression of Ang-2 nucleic acid or polypeptide coupled to an agent capable of causing vascular endothelial cell death.

27. The kit of claim 25 wherein the Ang-2 and the molecule capable of detecting Ang-2 are nucleic acids.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78361 A3

(51) International Patent Classification[7]: A61K 51/08, 49/00, 47/48, A61P 35/00, 9/00

(21) International Application Number: PCT/US00/15732

(22) International Filing Date: 8 June 2000 (08.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/139,642 17 June 1999 (17.06.1999) US

(71) Applicant *(for all designated States except US)*: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US).

(72) Inventor; and
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(74) Agents: **PALLADINO, Linda, O.**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 et al. (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
9 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78361 A3

(54) Title: METHODS OF IMAGING AND TARGETING TUMOR VASCULATURE

(57) Abstract: Methods for imaging and targeting tumor vasculature are provided. Specifically, the methods for imaging and targeting tumor vasculature relate to using angiopoietin-2 (Ang-2) to image developing tumor vasculature and to target therapeutic agents to developing tumor vasculature. Kits for imaging and targeting tumor vasculature are also provided.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
REG 334-A-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 15732	08/06/2000	17/06/1999
Applicant		
REGENERON PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 22-24, and part of 14-21 and 31-37

   Method for imaging tumor vasculature as claimed, and kits for this method

   1.1. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a conventional scintillation camera.

   1.2. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a gamma camera

   1.3. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a rectilinear scanner

   1.4. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a PET scanner

   1.5. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a SPECT scanner

   1.6. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a MRI or a NMR scanner

   1.7. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is an X-ray machine

2. Claims: 6, 8, 10-11, 25, 27, 29,
   and part of 14-21 and 31-37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method for causing tumor cell death as claimed, and kits for this method

3. Claims: 7, 9, 12-13, 26, 28, 30,
and part of 14-21 and 31-37

Method for causing vascular endothelial cell death as claimed, and kits for this method

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 1-5 are directed to a diagnostic method practised on the human/animal body, claims 6-13 to a method of treatment of the human/animal body, and claims 14-21 partially to each of such methods, a search has been carried out, based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1-37 in part

Present claims 1-37 concern a method (claims 1-21) or a kit (claims 22-37), in which the characterising element is defined by reference to a desirable characteristic or property, namely its ability to detect the peptide angiopoietine-2 or the nucleic acid encoding this peptide. The claims cover all methods or kits having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods or kits. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the methods or kits by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Also, the use of these type of definition in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Once again, the lack of clarity is such as to render a meaningful complete search impossible.
Finally, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the examples of the present application, as well as to angiopoietine-2 and its role in tumour genesis.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15732

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/08 A61K49/00 A61K47/48 A61P35/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, WPI Data, PAJ, MEDLINE, CANCERLIT, DISSERTATION ABS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 40947 A (RESOLUTION PHARMACEUTICALS INC., CAN.) 19 August 1999 (1999-08-19) example 16 claims 10,11,23	1-5, 14-24, 31-37
P,X	WO 00 18439 A (SCHERING AKTIENGESELLSCHAFT, GERMANY) 6 April 2000 (2000-04-06) page 3, line 13 -page 4, line 20 claim 3	1-5, 14-24, 31-37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	07/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Dullaart, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ASAHARA T ET AL: "TIE2 RECEPTOR LIGANDS, ANGIOPOIETIN-1 AND ANGIOPOIETIN-2, MODULATE VEGF-INDUCED POSTNATAL NEOVASCULARIZATION" CIRCULATION RESEARCH,US,GRUNE AND STRATTON, BALTIMORE, vol. 83, no. 3, 1998, pages 233-240, XP000907290 ISSN: 0009-7330 abstract page 234, right-hand column, paragraph RESULTS page 239, left-hand column, last paragraph -right-hand column, line 3 ---	6
X	LIN P ET AL: "ANTIANGIOGENIC GENE THERAPY TARGETING THE ENDOTHELIUM-SPECIFIC RECEPTOR TYROSINE KINASE TIE2" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 95, July 1998 (1998-07), pages 8829-8834, XP000857192 ISSN: 0027-8424 abstract page 8831, left-hand column, paragraph RESULTS page 8834, left-hand column ---	6
X	TANAKA S ET AL: "BIOLOGIC SIGNIFICANCE OF ANGIOPOIETIN-2 EXPRESSION IN HUMAN HEPATOCELLULAR CARCINOMA" JOURNAL OF CLINICAL INVESTIGATION,NEW YORK, NY,US, vol. 103, no. 3, 1999, pages 341-345, XP000929336 ISSN: 0021-9738 abstract page 343, left-hand column page 345, left-hand column --- -/--	1-37

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	MOLEMA GRIETJE ET AL: "The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy." JOURNAL OF CONTROLLED RELEASE, vol. 64, no. 1-3, 14 February 2000 (2000-02-14), pages 229-239, XP004185107 ISSN: 0168-3659 page 235, paragraph 9 -page 236, right-hand column, line 7 figure 1	1-37
O,X	& PROCEEDINGS OF THE FIFTH EUROPEAN SYMPOSIUM ON CONTROLLED DRUG DELIVERY, 1 - 3 April 1998, NOORDWIJK AAN ZEE, NETHERLANDS ---	1-37
X	BERNS A: "Mouse models for cancer at center stage - AACR special meeting: Cancer Biology and the Mutant Mouse: New Methods, New Models, New Insights, Keystone Colorado, USA, 31 January - 5 February 1999 " TRENDS IN GENETICS, vol. 15, no. 5, 1 May 1999 (1999-05-01), page 177 XP004167929 ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL ISSN: 0168-9525 right-hand column ---	1-37
X	LAUREN JUHA ET AL: "Is angiopoietin-2 necessary for the initiation of tumor angiogenesis?" AMERICAN JOURNAL OF PATHOLOGY, vol. 153, no. 5, November 1998 (1998-11), pages 1333-1339, XP000979136 ISSN: 0002-9440 page 1334, right-hand column, line 28 - line 30 figure 1 page 1337, left-hand column, line 21 -right-hand column, line 6 --- -/--	1-37

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	STRATMANN ASTRID ET AL: "Cell type-specific expression of angiopoietin-1 and angiopoietin-2 suggests a role in glioblastoma angiogenesis." AMERICAN JOURNAL OF PATHOLOGY, vol. 153, no. 5, November 1998 (1998-11), pages 1459-1466, XP000979137 ISSN: 0002-9440 abstract page 1462, right-hand column, last paragraph page 1463, left-hand column, line 1 - line 14 page 1465, right-hand column	1-37
X	WONG M P ET AL: "Down-regulated angiopoietin-1/tie-2 receptor pathway and enhanced expression of vascular endothelial growth factor and angiopoietin-2 in non-small cell lung carcinomas." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 556, abstract no. 3666 XP002158781 & 90th Annual Meeting of the American Association for Cancer Research; Philadelphia, Pennsylvania, USA; April 10-14, 1999 ISSN: 0197-016X abstract	1-37
X	DING H ET AL: "Expression and hypoxic regulation of angiopoietins and its receptors in human astrocytoma cell lines and tumor specimens." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 556, ABSTRACT NO. 3664 XP002158782 & 90th Annual Meeting of the American Association for Cancer Research; Philadelphia, Pennsylvania, USA; April 10-14, 1999 ISSN: 0197-016X abstract	1-37

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	CHAN A S Y ET AL: "Angiopoietin-2 and VEGF co-express in the accelerated phase of angiogenesis during anaplastic progression of gliomas." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 414, ABSTRACT NO. 2738 XP002158783 & 90th Annual Meeting of the American Association for Cancer Research; Philadelphia, Pennsylvania, USA; April 10-14, 1999 ISSN: 0197-016X abstract --- FUJIKAWA K ET AL: "Expression of angiopoietin 1, angiopoietin 2, tie 1 and tie 2 receptors in breast cancer." BLOOD, vol. 92, no. 10 SUPPL. 1 PART 1-2, 15 November 1998 (1998-11-15), page 174A, abstract no. 703 XP000979182 & 40th Annual Meeting of the American Society of Hematology; Miami Beach, Florida, USA; December 4-8, 1998 ISSN: 0006-4971 abstract --- HOLASH J ET AL: "Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF." SCIENCE (WASHINGTON D C), vol. 284, no. 5422, 18 June 1999 (1999-06-18), pages 1994-1998, XP002158988 ISSN: 0036-8075 abstract figures page 1997, left-hand column, last paragraph -page 1998, left-hand column, line 3 --- -/--	1-37 1-5, 14-24, 31-37 1-37

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	ZAGZAG DAVID ET AL: "In situ expression of angiopoietins in astrocytomas identifies angiopoietin-2 as an early marker of tumor angiogenesis." EXPERIMENTAL NEUROLOGY, vol. 159, no. 2, October 1999 (1999-10), pages 391-400, XP000979183 ISSN: 0014-4886 abstract page 393, right-hand column, paragraph RESULTS -page 395, left-hand column, line 4 page 396, left-hand column, last paragraph -right-hand column, line 8 page 399, left-hand column ---	1-37
P,X	YOSHIDA YUKIKO ET AL: "Expression of angiostatic factors in colorectal cancer." INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 15, no. 6, December 1999 (1999-12), pages 1221-1225, XP000979115 ISSN: 1019-6439 abstract page 1222, left-hand column, paragraph RESULTS -right-hand column, line 4 page 1223, right-hand column, last paragraph ---	1-37
P,X	HOLASH J ET AL: "New model of tumor angiogenesis: Dynamic balance between vessel regression and growth mediated by angiopoietins and VEGF." ONCOGENE, vol. 18, no. 38, pages 5356-5362, XP000979138 ISSN: 0950-9232 abstract figure 1 page 5358, right-hand column, last paragraph -page 5360, left-hand column, line 23 ---	1-37
P,X	IJLAND S A J ET AL: "Expression of angiogenic and immunosuppressive factors by uveal melanoma cell lines." MELANOMA RESEARCH, vol. 9, no. 5, October 1999 (1999-10), pages 445-450, XP000979142 ISSN: 0960-8931 page 449, left-hand column, line 47 - line 35 page 449, right-hand column, last paragraph --- -/--	1-37

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	THEIS HENRICH ET AL: "Role of VEGF, angiopoietins and their receptors in angiogenesis of renal cell carcinoma." JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 10, no. PROGRAM AND ABSTR. ISSUE, September 1999 (1999-09), page 186A, abstract no. A0951 XP000979139 & 32nd Annual Meeting of the American Society of Nephrology; Miami Beach, Florida, USA; November 1-8, 1999 ISSN: 1046-6673 abstract	1-37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/15732

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9940947 A	19-08-1999	AU 2406699 A	30-08-1999
		EP 1056773 A	06-12-2000
WO 0018439 A	06-04-2000	DE 19845798 A	13-04-2000
		AU 1264200 A	17-04-2000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 22-24, and part of 14-21 and 31-37

   Method for imaging tumor vasculature as claimed, and kits for this method

   1.1. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a conventional scintillation camera.

   1.2. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a gamma camera

   1.3. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a rectilinear scanner

   1.4. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a PET scanner

   1.5. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a SPECT scanner

   1.6. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is a MRI or a NMR scanner

   1.7. Claims: 1-5, 14-24 and 31-37 in part
   Method for imaging tumor vasculature as claimed, and kits for this method, in which the detector is an X-ray machine

2. Claims: 6, 8, 10-11, 25, 27, 29,
   and part of 14-21 and 31-37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method for causing tumor cell death as claimed, and kits for this method

3. Claims: 7, 9, 12-13, 26, 28, 30,
and part of 14-21 and 31-37

Method for causing vascular endothelial cell death as claimed, and kits for this method

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 1-5 are directed to a diagnostic method practised on the human/animal body, claims 6-13 to a method of treatment of the human/animal body, and claims 14-21 partially to each of such methods, a search has been carried out, based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1-37 in part

Present claims 1-37 concern a method (claims 1-21) or a kit (claims 22-37), in which the characterising element is defined by reference to a desirable characteristic or property, namely its ability to detect the peptide angiopoietine-2 or the nucleic acid encoding this peptide. The claims cover all methods or kits having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods or kits. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the methods or kits by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Also, the use of these type of definition in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Once again, the lack of clarity is such as to render a meaningful complete search impossible.
Finally, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the examples of the present application, as well as to angiopoietine-2 and its role in tumour genesis.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.